Patent
Attorney's Docket No.1034123-000122

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of	**MAIL STOP Amendment**
David Feifel	Group Art Unit: 1649
Application No.: 10/538,245	Examiner: Aditi DUTT
Filed: June 7, 2005	Confirmation No.: 3580
For: METHOD OF INHIBITING NEURAL TRANSMISSION MEDIATED BY SEROTONIN-2A AND ENHANCING SENSORIMOTOR GATING	Certificate of Mailing I hereby certify that this correspondence is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 C.F.R. §1.10, Express Mail Label No. EV 892 880 923 US, on January 3, 2008 and is addressed to the Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450. By: Kim A. Cabello

DECLARATION UNDER 37 C.F.R. § 1.131

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

1. I, David Feifel, having an address at 8241 La Jolla Scenic Drive North, La Jolla, California, 92037 am the inventor of the above-captioned United States Patent Application Serial No.10/538,245, which claims priority to International Patent Application Serial No. PCT/US03/039196, filed December 8, 2003 and United States Provisional Patent Application No. 60/431,937, filed December 9, 2002.

2. I am familiar with the prosecution history of Patent Application Serial No. 10/538,245. I understand that Hedley et al. is being cited as a reference against the claims of the application because Hedley et al. allegedly teaches the claimed invention prior to my invention date.

3. I submit that Hedley, et al. (Society for Neuroscience, 2002, Online) is not available as prior art under 35 U.S.C §102 or §103, because the publication is not prior to my invention date.

4. I submit that I conceived of the use of NT69L as a modulator of schizophrenia and other neuropsychiatric problems prior to Hedley et al. (published August 2002) and that I was diligent in reducing the claimed invention to practice up to and including the filing date of U.S. Patent Application No. 60/431,937, filed on December 9, 2002.

5. Evidence of the conception of the claimed invention is supplied in the form of a copy of notes (Exhibit A) from my laboratory notebooks, prior to August 2002, the publication date of Hedley et al. These notes show the reduction to practice of NT69L in the rat model of schizophrenia (the same model used by Hedley et al. in the publication being cited after my invention date).

Prior to the public availability of Hedley et al. (August 2002), the testing and identification of NT69L as a potential modulator of schizophrenia, bipolar disorders, anxiety and depression in rat models was first performed by me or under my direction at the University of California, San Diego, using an accepted rat model having reduced prepulse inhibition. I, or my technicians at my direction, first tested NT69L in the rat pre-pulse inhibition model startle reflex assay as early, and earlier than, July 2002, prior to Hedley et al.'s publication.

The laboratory pages of Exhibit A show dose calculations for NT69L and Rat Startle Run Sheets generated prior to August 2002. The Rat Startle Run Sheets demonstrate measurements of control and test groups in the prepulse inhibition (PPI) of the acoustic startle response rat model, one of the models used in Hedley et al. These experiments were carried out prior to August 2002.

I was diligent from the time of conception of the invention with respect to the use of neurotensin agonists including NT69L in the treatment of various psychotic disorders including bipolar, anxiety, depression and schizophrenia prior to August 2002 until the filing of the priority application on December 9, 2002.

6. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful

false statements and the like so made are punishable by fine or imprisonment, or both under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Respectfully submitted,

Date January 02 08

David Feifel

Rat Startle Run Sheet
NT69 / DOI

Experiment #: DF92D1

Date: [redacted]

Session: ElSOCRIT/LOCOMOTOR (DF92D1)

Run By: KP

Comments:

Protocol # 5-062-06
Runs # 1-6 up @ 7:30am
Runs # 7+8 up @ 8:33am

Groups:	NT69	DOI
(white)	1 = saline	1 = saline
(yellow)	2 = 0.01 mg/kg	2 = 0.5 mg/kg (whit
(orange)	3 = 0.1 mg/kg	
(red)	4 = 1.0 mg/kg	

Comments	LOCO Cage #	Box	Rat #	Group	Weight	(20min) LOCO Time 1	SC inj NT	(30 min) LOCO Time 2	SC inj DOI	(20min) LOCO Start time	(60min) PPI	(20min) LOCO Fin	File Name	
	1	1	10	1 1	298	8:00	8:20	8:22	8:52	8:54	9:15	9:36	df92d1r1	✓
	2	2	12	2 2	278	(1-10)		(12-26)		(28-37)		(49-58)		
	3	3	2	3 1	330	↓		↓		↓	↓	↓		
	4	4	5	4 2	284	8:20	↓	8:52	↓	9:14	9:35	9:56		
	5	1	3	1 2	302	8:26	8:46	8:48	9:18	9:20	9:41	10:02	df92d1r2	✓
	6	2	8	2 1	269	(14-23)		(25-39)		(41-50)		(62-71)		
	7	3	7	3 2	297	↓		↓		↓	↓	↓		
	8	4	1	4 1	290	8:46	↓	9:18	↓	9:40	10:01	10:22		
	9	1	6	4 2	281	8:52	9:12	9:14	9:44	9:46	10:07	10:28	df92d1r3	✓
	10	2	18	1 1	299	(27-36)		(38-52)		(54-63)		(75-84)		
	11	3	13	2 2	288	↓		↓		↓	↓	↓		
	12	4	4	3 1	302	9:12	↓	9:44	↓	10:06	10:27	10:48		
	1	1	21	4 1	309	10:00	10:20	10:22	10:52	10:54	11:15	11:36	df92d1r4	✓
	2	2	14	1 2	297	(61-70)		(72-86)		(88-97)		(109-118)		
	3	3	17	2 1	297	↓		↓		↓	↓	↓		
	4	4	9	3 2	281	10:20	↓	10:52	↓	11:14	11:35	11:56		
	5	1	25	3 1	287	10:26	10:46	10:48	11:18	11:20	11:41	12:02	df92d1r5	✓
	6	2	29	4 2	304	(74-83)		(85-99)		(101-110)		(122-131)		
	7	3	23	1 1	297	↓		↓		↓	↓	↓		
	8	4	22	2 2	288	10:46	↓	11:18	↓	11:40	12:01	12:22		
	9	1	16	3 2	295	10:52	11:12	11:14	11:44	11:46	12:07	12:28	df92d1r6	✓
	10	2	24	4 1	290	(87-96)		(98-112)		(114-123)		(135-144)		
	11	3	27	1 2	287	↓		↓		↓	↓	↓		
	12	4	19	2 1	309	11:12	↓	11:14	↓	12:06	12:27	12:48		
	1	1	35	2 2	289	12:00	12:20	12:22	12:52	12:54	1:15	1:36	df92d1r7	✓
	2	2	31	3 1	255	(121-130)		(133-146)		(148-157)		(169-178)		

Experiment #: DF92D1

Date: [redacted]

Session: EISOCRIT/LOCOMOTOR

Run By: KP

Comments: Protocol # 5-062-06

Rat Startle Run Sheet

NT69 / DOI

Groups:

NT69	DOI
1=saline	1=saline
2=0.01 mg/kg	2=0.5 mg/kg
3=0.1 mg/kg	
4=1.0 mg/kg	

Comments	loco cage#	Box	Rat #	Group	Weight	Time 1 (20min) LOCO	SC inj NT	Time 2 (30min) LOCO	SC inj DOI	Start time (20min) LOCO	(20min) PPI	(20min) LOCO	File Name	
	5	1	20	21	286	12:26	12:46	12:48	1:18	1:20	1:41	2:02	df92d1r8	✓
	6	2	30	32	288	(134-143)	↓	(145-159)	↓	(161-170)	↓	(182-191)		
	7	3	26	41	295	↓	↓	↓	↓	↓	↓	↓		
	8	4	34	12	280	12:46	↓	1:18	↓	1:40	2:01	2:22		
		1												
		2												
		3												
		4												
		1												
		2												
		3												
		4												
		1												
		2												
		3												
		4												
		1												
		2												
		3												
		4												
		1												
		2												
		3												
		4												
		1												
		2												

DF92 D1 NT69/DOI

DOI (0.5 mg/kg)

need:

$(16\ \text{rats})\left(\frac{0.5\ \text{mg}}{\text{kg}}\right)\left(\frac{0.5\ \text{kg}}{\text{rat}}\right) = 4\ \text{mg DOI}$

weigh:

$0.00422\ \text{g} = \frac{4.22\ \text{mg}}{0.5\ \text{mg/ml}} =$ add: 8.44 ml saline

NT69 (0.01, 0.1, 1.0 mg/kg)

need:

(8 rats) (1.0 mg/kg) (0.5 kg/rat) = 4 mg
(8 rats) (0.1 mg/kg) (0.5 kg/rat) = 0.4 mg
(8 rats) (0.01 mg/kg) (0.5 kg/rat) = 0.04 mg

need: 4.44 mg NT69

weigh:

$0.00497\ \text{g} = 4.97\ \text{mg}$

HIGH (1.0 mg/kg) $\frac{4.97\ \text{mg}}{1.0\ \text{mg/ml}} =$ add: 4.97 ml saline − 0.44 ml = HIGH 8 rats 4.53 ml (at least 4 ml)

MID (0.1 mg/kg) take 0.44 ml (at least 0.44) × 9 = 3.96 ml saline
+ 0.44 ml
4.40 ml T.V. − 0.4 ml = MID 8 rats 4.0 ml

LOW (0.01 mg/kg) take 0.4 ml (at least 0.4 ml) × 9 = 3.60 ml saline
+ 0.40 ml
4.00 ml T.V. LOW 8 rats

Experiment #: DF92 BL

Rat Startle Run Sheet

NT69/DOI Baseline

Groups: 99 = no drug

Date: [redacted]

Session: EISOCRIT / LOCOMOTOR

Run By: KP

Comments:
Protocol # 5-062-06

(60 min) LOCO

(20 min) EISOCRIT

Comments	LOCO cage #	Box	Rat #	Group	Weight	Time 1	Time 2	Start time	File Name	
	1	1	1	99	289		1:00	2:02	df92b1 r1	✓
	2	2	2		313					
	3	3	3		291					
	4	4	4	↓	290		↓ 2:00	↓ 2:22		
	5	1	5	99	277		1:24	2:26	df92b1 r2	✓
	6	2	6		274					
	7	3	7		290					
	8	4	8	↓	266		↓ 2:24	↓ 2:46		
	9	1	9	99	277		1:48	2:50	df92b1 r3	✓
	10	2	10		293					
	11	3	11		276					
	12	4	12	↓	277		↓ 2:48	↓ 3:10		
	1	1	13	99	282		2:12	3:14	df92b1 r4	✓
	2	2	14		286					
	3	3	15		294					
	4	4	16	↓	286		↓ 3:12	↓ 3:34		
	5	1	17	99	295		2:36	3:38	df92b1 r5	✓
	6	2	18		289					
	7	3	19		298					
	8	4	20	↓	284		↓ 3:36	↓ 3:58		
	9	1	21	99	300		3:00	4:02	df92b1 r6	✓
	10	2	22		283					
	11	3	23		292					
	12	4	24	↓	282		↓ 4:00	↓ 4:22		
	1	1	25	99	276		3:24	4:26	df92b1 r7	✓
	2	2	26	↓	287					

Experiment #: DF92BL

Rat Startle Run Sheet

NT69/DOI Baseline

Groups: 99=no drug

Date: [redacted]

Session: EISOCRIT/LOCOMOTOR

Run By: KP

Comments:

Protocol #5-062-06

Comments	loco cage #	Box	Rat #	Group	Weight	Time 1	Time 2 (60min) LOCO	Start time (20 min) EISOCRIT	File Name	
	5	1	29	99	292		3:48	4:50	df92b1 r8	✓
	6	2	30	↓	279		↓	↓		
	7	3	31	↓	256		↓	↓		
	8	4	32	↓	283		4:48	5:10		
	9	1	33	99	277		4:12	5:14	df92b1 r9	✓
	10	2	34	↓	276		↓	↓		
	11	3	35	↓	280		↓	↓		
	—	4	99	99	—		5:12	5:34		
		1								
		2								
		3								
		4								
		1								
		2								
		3								
		4								
		1								
		2								
		3								
		4								
		1								
		2								
		3								
		4								
		1								
		2								

Experiment #: DF92D2

Date: [redacted]

Session: ELISOCRIT/LOCOMOTOR (DF92D2)

Run By: KP

Rat Startle Run Sheet

NT69/ DOI

* Flip DOI Group *

Groups:	NT69:	DOI
	1 = saline	1 = saline
	2 = 0.2mg/kg	2 = 0.5mg/kg
	3 = 0.1mg/kg	
	4 = 1.0mg/kg	

Comments:

Protocol # 5-062-06

Run 1: F 1-6 up @ 6:58 am

Run #2: 7 & 8 up @ 7:07 am

Comments:	loco cage #	Box	Rat #	Group	Weight	(20 min) LOCO Time 1	SC: PPI NT	(20 min) LOCO Time 2	SC: PPI DOI	(20 min) LOCO Start time	(20 min) PPI	(20 min) LOCO File Name	
	1	1	10	12	322	7:28	7:48	7:50	8:20	8:22	8:43	9:04	df92d2r1 ✓
	2	2	12	21	302	(1-10)	|	(12-26)	|	(28-37)	|	(49-58)	
	3	3	2	32	354	↓	|	↓	|	↓	↓	↓	
	4	4	5	41	315	7:48	↓	8:20	↓	8:42	9:03	9:24	
	5	1	3	11	319	7:54	8:14	8:16	8:46	8:48	9:09	9:30	df92d2r2 ✓
	6	2	8	22	281	(4-23)	|	(25-39)	|	(41-50)	|	(62-71)	
	7	3	7	31	318	↓	|	↓	|	↓	↓	↓	
	8	4	1	42	306	8:14	↓	8:46	↓	9:08	9:29	9:50	
* 1st loco started 2 min late *	9	1	6	41	295	~~8:20~~ 8:22	8:40	8:42	9:12	9:14	9:35	9:56	df92d2r3 ✓
	10	2	18	12	324	(27-36)	|	(38-52)	|	(54-63)	|	(75-84)	
	11	3	13	21	300	↓	|	↓	|	↓	↓	↓	
	12	4	4	32	325	8:40	↓	9:12	↓	9:34	9:55	10:16	
	1	1	21	42	322	9:28	9:48	9:50	10:20	10:22	10:43	11:04	df92d2r4 ✓
	2	2	14	11	306	(61-70)	|	(77-86)	|	(88-97)	|	(109-118)	
	3	3	17	22	319	↓	|	↓	|	↓	↓	↓	
	4	4	9	31	297	9:48	↓	10:20	↓	10:42	11:03	11:24	
	5	1	25	32	298	9:54	10:14	10:16	10:46	10:48	11:09	11:30	df92d2r5 ✓
	6	2	29	41	313	(74-83)	|	(85-99)	|	(101-110)	|	(122-131)	
	7	3	23	12	312	↓	|	↓	|	↓	↓	↓	
	8	4	22	21	302	10:14	↓	10:46	↓	11:08	11:29	11:50	
	9	1	16	31	309	10:20	10:40	10:42	11:12	11:14	11:35	11:56	df92d2r6 ✓
	10	2	24	42	297	(87-96)	|	(98-112)	|	(114-123)	|	(135-144)	
	11	3	27	11	303	↓	|	↓	|	↓	↓	↓	
	12	4	19	22	334	10:40	↓	11:12	↓	11:34	11:55	12:16	
	1	1	35	21	309	11:28	11:48	11:50	12:20	12:22	12:43	1:04	df92d2r7 ✓
	2	2	31	32	264	(121-130)	|	(132-146)	|	(148-157)	|	(169-178)	

Acoustic Startle Run Sheet

NT69/DOI

Experiment #: DF92D2

Date: [redacted]

Session: E'ISOCRIT/LOCOMOTOR *Flip DOI Group*

Run By: KP

Comments:
Protocol #5-062-06

Groups:

NT69	DOI
1 = saline	1 = saline
2 = 0.01 mg/kg	2 = 0.5 mg/kg
3 = 0.1 mg/kg	
4 = 1.0 mg/kg	

Comments	Box	Rat #	Group	Weight	Time 1 (20 min) LOCO	SC inj NT	Time 2 (30 min) LOCO	SC inj DOI	Start time (20 min) LOCO	(20 min) PPI	File (20 min) LOCO	Name	
5	1	20	22	305	11:54	12:14	12:16	12:46	12:48	1:09	1:30	df92d2r8	✓
6	2	30	31	302	(134-143)	↓	(145-199)	↓	(161-170)	↓	(182-191)		
7	3	26	42	304	↓		↓		↓	↓	↓		
8	4	34	11	300	12:14	↓	12:46	↓	1:08	1:29	1:50		
	1												
	2												
	3												
	4												
	1												
	2												
	3												
	4												
	1												
	2												
	3												
	4												
	1												
	2												
	3												
	4												
	1												
	2												
	3												
	4												
	1												
	2												

DF92D2 NT69/DOI

DOI (0.5 mg/kg)

need: 4 mg DOI

weigh:
0.00462 g = 4.62 mg / 0.5 mg/ml = add: 9.24 ml saline

NT69 (0.01, 0.1, 1.0 mg/kg)

need: 4.44 mg NT69

weigh:
0.00500 g = 5.00 mg

HIGH (1.0 mg/kg): 5.00 mg / 1.0 mg/ml = add: 5.00 ml saline − 0.44 ml = 4.56 ml — HIGH 8 rats

MID (0.1 mg/kg): take 0.44 ml × 9 = 3.96 ml saline
+ 0.44 ml
4.40 ml T.V. − 0.4 ml = 4.0 ml — MID 8 rats

LOW (0.01 mg/kg): take 0.40 ml × 9 = 3.6 ml saline
+ 0.4 ml
4.0 ml T.V — LOW 8 rats